

DETAILED ACTION

Application status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/06/2009 has been entered.

In response to the previous Office action, a final rejection (mailed on 10/08/2008), Applicants filed a response and amendment received on 04/06/2009. Said amendment canceled Claims 13-28, 33, 34 and 36-39, and amended Claims 1-8, 10, 11, 29-32 and 40-45. Thus, Claims 1-12, 29-32, 35 and 40-45 are at issue and present for examination.

Applicants' arguments filed on 04/06/2009, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

The previous objection of Claims 1, 2, 40 and 41 for the recitation of "shown in Figure 5a (SEQ ID NO: 1)", is withdrawn by virtue of Applicants' amendment to the language suggested by the Examiner, ---as set forth in SEQ ID NO: 1---.

The previous objection of Claims 1, 6, 29, 40 and 44 for containing a misspelling in "3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid" (underlined for added emphasis) is withdrawn by virtue of Applicants' amendment. The Examiner suggests replacing it with "3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid."

The previous objection of Claims 4, 5 and 7 for the recitation of "wherein said crystal belongs to space group ...," is withdrawn by virtue of Applicants' amendment which replaced the noted phrase with "wherein said crystal ... has".

The previous objection of Claims 10 and 40 for the recitation of "NR box of TIF2" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claims 29 and 30 for containing typographical errors, i.e., "Thr2n" and "Va1439", is withdrawn by virtue of Applicants' amendment.

The previous objection of Claims 29 and 30 for containing typographical errors, i.e., "form", is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 31 for the recitation of "in Figure 5a (SEQ ID NO: 1)" and "in Figure 5b (SEQ ID NO: 2)", is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 42 for missing "angstrom" symbols after each unit cell dimensions a, b, and c, is withdrawn by virtue of Applicants' amendment.

Claims 2, 3-7, 11, 12, 31, 32, 35, 42, 44 and 45 are objected to because of the following informalities:

Claim 2 is objected to for the recitation of "the LXR β LBD in the crystal belonging to" because it can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ----the crystalline LXR β LBD has----

Claim 11 is objected to for the recitation of "A crystal according to any of claims 8-10" can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ---The crystal according to claim 8, 9 or 10---

Claims 12, 32 and 35 are objected to for the recitation of "A" or "An" at the start of each claim which can be substantially improved with respect to form. The Examiner suggests replacing such indefinite articles with ---The---

Claim 35 is objected to for the recitation of "the amino acid sequence used in a crystal according to claim 1," which can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ---the amino acid sequence of the human LXR β LBD according to claim 1---

Claims 3-7, 31 and 42 are objected to for depending from a rejected claim.

Claims 44 and 45 are objected to for containing typographical error in the recitation of "form". The Examiner suggests replacing the noted term with ---from---

Claims 44 and 45 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s)

in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "said amino acids" in claims 44 and 45 refers to the amino acid residues of the LXR β LBD recited in claim 29 and 30, respectively. As such, "the crystallized molecule or molecular complex of claim 29 [or 30] ... has the structural coordinates according to Table 2, or *having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å*" fails to further limit the subject matter a previous claim (emphasis added).

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of Claims 1, 2, 29, 30, 40-42, 44 and 45 (4-7, 35 and 43 dependent therefrom) for reciting the indefinite phrase, "LXR β ligand binding domain" or "LBD," is withdrawn because Applicants have defined the LBD as either consisting of or comprising amino acids 220-461 or 213-461 of SEQ ID NO: 1.

The previous rejection of Claims 1 and 40 (2-7, 11, 12 and 41 dependent therefrom) for reciting the indefinite phrase, "a polypeptide comprising [or having] an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of human LXR β (SEQ ID NO: 1)" is withdrawn because Applicants have deleted the noted phrase.

The previous rejection of Claim 7 for reciting the phrase, "wherein said crystal belongs to space group $P6_122$ and has the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 59 \pm 3 \text{ \AA}$, $c = 294 \pm 3 \text{ \AA}$ or $a=58.7\text{\AA}$, $b=98.9\text{\AA}$, $c=175.8\text{\AA}$ wherein $\alpha=\beta=90^\circ$, $\gamma=120^\circ$ " is withdrawn because Applicants' have deleted the phrase "or $a=58.7\text{\AA}$, $b=98.9\text{\AA}$, $c=175.8\text{\AA}$ ".

The previous rejection of Claim 32 for reciting an indefinite phrase, "such as his tag", is withdrawn because Applicants' have deleted the noted phrase.

The previous rejection of Claim 40 for reciting the phrase, "said LXR β ligand being chosen from ... or N-[1-(2- furanyl)ethyl]-N-4-pyridinyl-tricyclo [3.3.1.1^{3,7}] decane-1-carboxamide Liver X receptor beta ligand binding domain (LXR β LBD)" is withdrawn because Applicants have deleted the noted phrase.

The previous rejection of Claim 43 for reciting the phrase, "The crystallized molecule or molecular complex of claim 29 or 30, wherein said binding pocket was resolved by molecular replacements using the structure of a thyroid hormone receptor as a search model" is withdrawn by virtue of Applicants' amendment which clarified that it is the structural coordinates that is resolved by molecular replacement.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

All of the previous rejections of Claims 1-12, 29, 30 and 40-45 under 35 U.S.C. § 112, first paragraph, written description, for containing new matter, are withdrawn

because Applicants have deleted that recitations of new matter, i.e., Claim 1: "a crystal belonging to space group $P6_122$, wherein said LXR β LBD comprises...a polypeptide comprising an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461"; Claim 6: "The crystal according to claim 1 or 3, further comprising 3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid bound to the LXR β LBD"; and Claim 7: "wherein said crystal belongs to space group $P6_122$ and has the unit cell dimensions ...or $a = 58.7 \text{ \AA}$, $b = 98.9 \text{ \AA}$, $c = 175.8 \text{ \AA}$ ".

Claims 8, 11 and 12 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 8 (11 and 12 dependent therefrom) is rejected for containing new matter because the specification does not provide support for a crystal of the Liver X receptor beta ligand binding domain (LXR β LBD) belonging to the space group $P2_12_12$ and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 100 \pm 5 \text{ \AA}$, $c = 176 \pm 3 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$ (emphasis added, see page 6 of the specification).

Claims 1, 2, 8-12, 29, 30, 40, 41 and 43-45 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-12, 29, 30 and 40-45. In response to this rejection, Applicants have canceled Claims 13-28, 33, 34 and 36-39, and amended Claims 1-8, 10, 11, 29-32 and 40-45, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Claims 8-10 (and claims dependent therefrom) are directed to crystals of the LXR β LBD, in apo- (unliganded) form or complexed to the particular ligand specified, having the exact space group and unit cell dimensions disclosed in the instant specification, e.g., in paragraphs 18-20, respectively, of US 07/0060740. Similarly, dependent claims 3-7 and 42 are directed to crystals of the LXR β LBD, in apo form or complexed to the particular ligand specified, that comprise or consist of the particular amino acid sequence of the LXR β LBD specified, and recite the exact space group and unit cell dimensions disclosed in the instant specification, e.g., in Table 1, paragraphs 125, 20 and 19, respectively, of US 07/0060740. Paragraphs 122-126 of US 07/0060740 describe experimental data with explanations on how to make and characterization of the claimed crystals. The scope of the genus encompassed by claims 3-10 and 42 (and its dependencies) is commensurate with the LXR β LBD crystal species disclosed by the Applicants. The recitation of the exact space group and unit cell dimensions in these claims provide ample structural features in common to support the breadth of the claims. It is undisputed that claims 3-10 and 42 in their present form

impose almost identical structural parameters as those specified by hypothetical claim 1 exemplified in case 4 of the "Trilateral Project WM4 Comparative Studies in New Technologies: Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims" released in November 2002 ("the Trilateral Report"). The USPTO indicated in the Trilateral Report that hypothetical claim 1 would meet the written description requirement because the crystal structure of the protein is provided in the claim by specifying the cell unit dimension. More specifically, claim 1 in case 4 of the Trilateral Report is directed to a crystalline form of a known protein P, and reads as follows: "A crystalline form of protein P having unit cell dimensions of $a=4.0\text{nm}$, $b=7.8\text{nm}$, and $c=1.0\text{nm}$." At pages 8 and 66 of the report, the hypothetical specification of case 4 is described as including, inter alia, that the inventors have newly produced a stable crystalline form of protein P and that the description gives experimental data with explanations of how to make the crystals. The Trilateral Report, at page 67, referring to the claim of case 4, states that "the claim complies with the written description requirement because the structure of protein P is provided." (emphasis added). Like the hypothetical claim 1 presented in case 4 of the Trilateral Report, claims 3-10 and 42 are directed to a crystalline form of a specific known protein (i.e., LXR β LBD), which was characterized in the art prior to the filing date in terms of its structure and function. Also similar to the hypothetical claim 1 presented in case 4, instant claims 3-10 recite the unit cell dimensions of the crystal. The present specification discloses, inter alia, that the inventors had newly produced six crystalline forms of LXR β LBD, provided LXR β LBD sequence and ligand structural information, experimental data with explanations on how

to make the crystals, and the three-dimensional structure of a crystalline form of the LXR β LBD polypeptide (see specification at, e.g., paragraphs 17-21, 117-126 (including Table 1 and Figures 5a-7 of US 07/0060740). Applicants clarify that at least the following species of LXR β LBD, in apo or complexed form, were disclosed in the instant application as filed: 2 species of crystals of LXR β LBD complexed with T0901317 or GW3965 having space group P212121 are disclosed in Table 1 of US 07/0060740; 2 species of crystals of LXR β LBD in apo form or complexed with T0901317 having space group P6122 are disclosed in paragraph 19 and 125, respectively, of US 07/0060740; 2 species of crystals of LXR β LBD in apo form or complexed with the NR-box of TIF having space group P21212 are disclosed in paragraphs 18 and 20, respectively, of US 07/0060740. Thus, Applicants respectfully submit that for at least the reasons set forth above, the specification amply provides written description for the crystalline forms of LXR β LBD polypeptide as presently set forth in claims 3-10 and 42. The remaining claims also comply with the written description requirement. For example, claims 1 and 40 require the LXR β LBD crystal to be complexed to a particular ligand and to have the space group specified (namely, P212121, P6122 and P21212), in addition to the LXR β LBD amino acid sequence specified. Claims 2 and 41 are directed to LXR β LBD crystals having the structural parameters of the base claim, wherein the LXR β LBD polypeptide sequence "consists of" the amino acid sequence disclosed in SEQ ID NO: 1. Similarly, claims 29-30 and 43-45 require the LXR β LBD crystal to be complexed to a particular ligand and to include the binding pocket having the structural coordinates of Table 2 within the deviation specified, in addition to the LXR β LBD amino acid sequence

specified. Therefore, these claims specify sufficient common attributes of the claims crystals, in terms of space groups, structural coordinates and LXR β LBD amino acid sequence to be fully supported by the six members of the genus of LXR β LBD crystals disclosed by the Applicants. The Office is reminded that a description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. In sum, the scope of the aforementioned genus encompassed by the claims does not have substantial variation in view of the claims' precise structural parameters specified by the claims. Given the defined scope of the claims, Applicants respectfully submit that the specification provides ample number of species having a common attribute to show that the applicants were in possession of the claimed crystals and methods.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of claims are analyzed to assess how the genera of inventions as claimed fail to meet the written description requirement under the 35 USC 112 1st paragraph.

The scope of claim 1 encompasses a genus of (A) crystal complexes of LXR β LBD bound to N-(2,2,2-trifluoroethyl)-N-[4[2,2- trifluoro-l-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide, belonging to space group P2₁2₁2₁, wherein said LXR beta LBD consists of the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of the human LXR beta as set forth in SEQ ID NO: 1, *optionally having any unit cell dimensions and any bond angles*; or (B) crystal

complexes of LXR β LBD bound to 3-(3-(2-chloro-3-trifluoromethylbenzyl)- 2,2-diphenylethylamino)propoxy)phenylacetic acid belonging to space group P6₁22, wherein said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of the human LXR beta as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; or (C) crystal complexes of LXR β LBD bound to N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide, said crystal complex belonging to space group P6₁22, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 of [a] the human LXR β as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; (d) crystals of LXR β LBD belonging to space group P6₁22, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 of the human LXR β as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; and (e) crystal complexes of LXR β LBD bound to a coactivator peptide Nuclear Receptor (NR) box 1 of Transcription Intermediary Factor 2 (TIF2), said crystal complexes belonging to space group P2₁2₁2, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of the human LXR β as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences*

attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles (italicized for added emphasis).

The scope of claim 8 encompasses a genus of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) belonging to the space group $P2_12_12$ and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 100 \pm 5 \text{ \AA}$, $c = 176 \pm 3 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, *wherein said LXR β LBD has any amino acid residues of LXR β that are capable of binding a ligand*

The scope of claim 9 encompasses a genus of crystals of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) belonging to the space group $P6_122$ and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 59 \pm 3 \text{ \AA}$, $c = 294 \pm 3 \text{ \AA}$, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, *wherein said LXR β LBD has any amino acid residues of LXR β that are capable of binding a ligand*.

The scope of claim 10 encompasses a genus of crystals of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) in complex with a coactivator peptide Nuclear Receptor (NR) box 1 of Transcription Intermediary Factor 2 (TIF2) belonging to the space group $P2_12_12$, and having the unit cell dimensions $a = 89 \pm 3 \text{ \AA}$, $b = 91 \pm 3 \text{ \AA}$, $c = 131 \pm 3 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, *wherein said LXR β LBD has any amino acid residues of LXR β that are capable of binding a ligand*.

The scope of claim 29 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319,

Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the structural coordinates of the complex of LXR beta LBD and 3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.*

The scope of claim 30 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the complex LXR beta LBD and N-(2,2,2-trifluoroethyl)-N-[4[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.*

The scope of claim 40 encompasses crystals of the LXR beta LBD in complex with a coactivator peptide TIF2, wherein: said crystal belongs to space group P2₁2₁2₁; and said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta as set forth in SEQ ID NO: 1 having *any unit cell dimensions and any bond angles*.

In light of the notion that obtaining X-ray diffraction quality crystals is highly unpredictable (see previous enablement rejection with regard to the unpredictability associated with making X-ray diffraction quality crystals), the genera of crystals as explained above for each claim is not adequately described in the instant application as previously explained. In addition, as explained in the previous enablement rejection, the general knowledge in the art teaches that an amino acid sequence cannot be theoretically translated into a biologically relevant 3-D structure. Also, the Case 4 of the Trilateral Project WM4, is not analogous to the fact patterns of this instant application with regard to the protein structure of LXR β *Ligand Binding Domain*, *having any unit cell dimensions and any bond angles* (emphasis added). Even assuming arguendo that the crystal of claim 1 (a) meets the criteria as set forth in Case 4 of the Trilateral Project WM4 with regard to the LXR β LBD which *consists of the recited amino acids*, there is no limitations on unit cell dimensions of the crystal of Claim 1 (a), which clearly fails to meet the criteria as set forth in the Case 4 of the Trilateral Project WM4.

For these reasons, one of skill in the art would not have recognized that Applicants were in possession of the genera of crystals as claimed which represent the biologically relevant 3-D structures so that compounds can be screened against such

structures to identify a therapeutically useful compounds. It is noted by the Examiner that the specification only describes 4 X-ray diffraction quality crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claims 1, 2, 8-12, 29, 30, 40, 41 and 43-45 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a crystal, comprising X-ray diffraction quality crystal of human liver X receptor beta consisting of the contiguous amino acid residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 100 \pm 5 \text{ \AA}$, $c = 176 \pm 3 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, or alternatively has the space group $P6_122$ and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 59 \pm 3 \text{ \AA}$, $c = 294 \pm 3 \text{ \AA}$, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$ that diffracts x-rays to a resolution of less than or equal to 3 angstroms, does not reasonably provide enablement for any crystals as described in the rejection under 112 1st paragraph, written description. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-12, 29, 30 and 40-45. In response to this rejection, Applicants have canceled

Claims 13-28, 33, 34 and 36-39, and amended Claims 1-8, 10, 11, 29-32 and 40-45, and traverse the rejection as it applies to the newly amended claims.

Applicants clarify for the record that at least the following species of LXR β LBD, in apo or complexed form, were successfully crystallized following the teaching of the specification as filed, namely, 2 species of crystals of LXR β LBD complexed with T0901317 or GW3965 having space group P212121 are disclosed in Table 1 of US 07/0060740; 2 species of crystals of LXR β LBD in apo form or complexed with T0901317 having space group P6122 are disclosed in paragraph 19 and 125, respectively, of US 07/0060740; 2 species of crystals of LXR β LBD in apo form or complexed with the NR-box of TIF having space group P21212 are disclosed in paragraphs 18 and 20, respectively, of US 07/0060740. Each of the grounds raised by the Office in maintaining the position that the claims are not enabled is discussed in more detail below. Applicants traverse the Office's maintained position that claims 8-10 (and claims dependent therefrom), which are directed to crystals of the LXR β LBD, in apo- (unliganded) form or complexed to the particular ligand specified, having the exact space group and unit cell dimensions exemplified in the instant specification, e.g., in paragraphs 18-20, respectively, of US 07/0060740, are not adequately enabled by the instant application. Similarly, dependent claims 3-7 and 42 are directed to crystals of the LXR β LBD, in apo form or complexed to the particular ligand specified, that comprise or consist of the particular amino acid sequence of the LXR β LBD specified, and recite the exact space group and unit cell dimensions disclosed in the instant specification, e.g., in Table 1, paragraphs 125, 20 and 19, respectively, of US 07/0060740. Paragraphs 122-

126 of US 0710060740 describe experimental data with explanations on how to make and characterization of the claimed crystals. The crystallization conditions and methods disclosed in the specification resulted in crystals having the space group and parameters encompassed by claims 8-10 and 42. Applicants do not understand the Office's position in rejecting these claims since the Office admits that the specification discloses "4 X-ray diffraction crystals" with the particular structural parameters encompassed by the claims, and those particular working examples are specified by these claims. Applicants also submit that claims 8-10 are commensurate in scope with exemplary claim 1 of case 4 of the Trilateral Report, which was deemed by the USPTO to satisfy the enablement requirement. More specifically, the Trilateral Report states that claims to a crystalline form of a polypeptide (e.g., like exemplary claim 1 of case 4) satisfy the enablement requirement, if the specification teaches how to make the claimed crystals and if one skilled in the art could use the claimed crystal without undue experimentation (see the Trilateral Report at page 67 and case 4 of the Trilateral Report at page 66). The instant specification discloses how to make the claimed compositions, e.g., in paragraphs 122-126 of US 0710060740, and one of skill in the art could have used the claimed crystal without undue experimentation. It is also noted for the record that none of claims 1-10 or 40-42 requires "X-ray diffraction quality crystals," "for use to identify therapeutic compounds" "for treatment of atherosclerosis," which the Office alleges are "highly unpredictable" to obtain, and that "one would have to painstakingly determine which of the genera of crystals as described above represent the biologically relevant 3-D structures so that structural studies can be performed in order to identify

and synthesize new therapeutic compounds for treatment of atherosclerosis by inducing cholesterol efflux from macrophages/foam cells." (See Office Action at pages 22-23).

Claims 1-10 and 40-42 are directed to crystals of LXR β LBD, in apo form or complexed to the particular ligand specified, that comprise or consist of the particular amino acid sequence of the LXR β LBD specified, and/or recite the exact space group and unit cell dimensions. Although Applicants reiterate that at least 6 X-ray-diffraction quality crystals were successfully obtained following the guidance provided in the instant specification (and thus, claims to x-ray quality crystals are fully enabled by the specification), claims 1-10 or 40-42 encompass both x-ray and non-x-ray quality crystals, both forms of which are fully enabled by the instant application. Similarly, the remaining claims are commensurate in scope with Applicants' disclosure. For example, claims 1 and 40 require the LXR β LBD crystal to be complexed to a particular ligand and to have the space group specified (namely, P212121, P6122 and P21212), in addition to the LXR β LBD amino acid sequence specified. Claims 2 and 41 are directed to LXR β LBD crystals having the structural parameters of the base claim, wherein the LXR β LBD polypeptide sequence "consists of" the amino acid sequence disclosed in SEQ ID NO:

1. Similarly, claims 29-30 and 43-45 require the LXR β LBD crystal to be complexed to a particular ligand and to include the binding pocket having the structural coordinates of Table 2 within the deviation specified, in addition to the LXR β LBD amino acid sequence specified. The genus of LXR β LBD polypeptides encompassed by these crystal claims does not have substantial variation, since all must encode a polypeptide comprising, or consisting of, the amino acid sequence specified. The specification teaches how to

make the claimed crystals, for example in paragraphs 122-126 of US 07/0060740. The amino acid sequence and domain characterization of LXR β LBD were known in the art at the time the instant application was filed and are described in the instant application. The structural coordinates of human LXR β LBD, in complex form, were set forth in Table 2 of the application. With respect to the state-of-the-art in generating LXR β LBD polypeptides, techniques for generating LXR β LBD polypeptides (and variants thereof) were known in the art and were performed routinely by molecular biologists at the time the present application was filed. The disclosure also describes and demonstrates methods for successfully crystallizing LXR β LBD polypeptides. Once the crystallization conditions are established, one of ordinary skill in the art could have practiced the claimed invention (which, as discussed above, is directed to the very specific LXR β LBD crystals generated following the conditions outlined in the specification), by routine experimentation. Therefore, Applicants submit that following the teachings of the specification, one of ordinary skill in the art would have been able to generate crystals of LXR β LBD polypeptide having the structural information encompassed by the claims by simply following the teachings of the specification. Applicants previously cited Itoh, S. I. and M. A. Navia (1995) Protein Science, (4), 2261- 2268 and Sauer, U. H., S. Dao-Pin, and B. W. Matthews (1992) Journal of Biological Chemistry (267) 2393-2399 as supporting the assertion that at the time the instant application was filed, it was known in the art that variants of proteins with known crystallization parameters were likely to readily crystallize with similar crystal structures as long as the variations introduced did not markedly affect intermolecular crystal contacts or amino acid residues important for

protein stability (i.e., within the hydrophobic core). Even mutations that had an effect in altering protein stability, such as inserting a proline amino acid, were found to crystallize with similar crystallization parameters as the native protein, emphasizing that well-folded proteins can exhibit crystallization properties similar to the non-mutated counterparts. Sauer, U. H., *supra*. Applicants submit that the numerous reference cited by the Office in support of the alleged unpredictability of the crystallography art are not relevant to the present claims in view of their scope. Applicants are claiming the particular LXR β LBD crystals that they prepared following the teachings in the specification. The application teaches how to make and use claimed crystals of LXR[3 LBD polypeptides, e.g., crystals of LXR β LBD polypeptides of 2 species of crystals of LXR β LBD complexed with T0901317 or GW3965 having space group P212121; 2 species of crystals of LXR β LBD in apo form or complexed with T0901317 having space group P6122; 2 species of crystals of LXR β LBD in apo form or complexed with the NR-box of TIF having space group P21212, and the reference sequence specified. Applicants had disclosed (and optimized) in the present application the crystallization conditions of the LXR β LBD polypeptide within the scope of the present claims. In view of the disclosure of the specification and the knowledge in the field of protein crystallography at the filing date, undue experimentation would not be required to make and use the subject matter covered by the claims.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of claims are analyzed to assess

how the genera of inventions as claimed fail to meet the enablement requirement under the 35 USC 112 1st paragraph.

The scope of claim 1 encompasses a genus of (A) crystal complexes of LXR β LBD bound to N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-l-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide, belonging to space group P2₁2₁2₁, wherein said LXR beta LBD consists of the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of the human LXR beta as set forth in SEQ ID NO: 1, *optionally having any unit cell dimensions and any bond angles*; or (B) crystal complexes of LXR β LBD bound to 3-(3-(2-chloro-3-trifluoromethylbenzyl)- 2,2-diphenylethylamino)propoxy)phenylacetic acid belonging to space group P6₁22, wherein said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of the human LXR beta as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; or (C) crystal complexes of LXR β LBD bound to N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-l-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide, said crystal complex belonging to space group P6₁22, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 of [a] the human LXR β as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; (d) crystals of LXR β LBD belonging to space group P6₁22, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 of the human LXR β as set forth in SEQ ID

NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles*; and (e) crystal complexes of LXR β LBD bound to a coactivator peptide Nuclear Receptor (NR) box 1 of Transcription Intermediary Factor 2 (TIF2), said crystal complexes belonging to space group P2₁2₁2, wherein said LXR β LBD comprises the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of the human LXR β as set forth in SEQ ID NO: 1, *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, having any unit cell dimensions and any bond angles* (italicized for added emphasis).

The scope of claim 8 encompasses a genus of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) belonging to the space group P2₁2₁2 and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 100 \pm 5 \text{ \AA}$, $c = 176 \pm 3 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, *wherein said LXR β LBD has any amino acid residues of LXR β that are capable of binding a ligand.*

The scope of claim 9 encompasses a genus of crystals of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) belonging to the space group P6₁22 and having the unit cell dimensions $a = 59 \pm 3 \text{ \AA}$, $b = 59 \pm 3 \text{ \AA}$, $c = 294 \pm 3 \text{ \AA}$, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, *wherein said LXR β LBD has any amino acid residues of LXR β that are capable of binding a ligand.*

The scope of claim 10 encompasses a genus of crystals of crystals of the Liver X receptor beta ligand binding domain (LXR β LBD) in complex with a coactivator peptide Nuclear Receptor (NR) box 1 of Transcription Intermediary Factor 2 (TIF2) belonging to

the space group $P2_12_12_1$ and having the unit cell dimensions $a = 89 \pm 3$ Å, $b = 91 \pm 3$ Å, $c = 131 \pm 3$ Å, $\alpha = \beta = \gamma = 90^\circ$, wherein said $LXR\beta$ LBD has any amino acid residues of $LXR\beta$ that are capable of binding a ligand.

The scope of claim 29 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the structural coordinates of the complex of LXR beta LBD and 3-(3-(2-chloro-3-trifluoromethylbenzyl)-2,2-diphenylethylamino)propoxy)phenylacetic acid as shown in Table 2, wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

The scope of claim 30 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the

complex LXR beta LBD and N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-l-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.*

The scope of claim 40 encompasses crystals of the LXR beta LBD in complex with a coactivator peptide TIF2, wherein: said crystal belongs to space group $P2_12_12_1$; and said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta as set forth in SEQ ID NO: 1 having *any unit cell dimensions and any bond angles.*

In light of the notion that obtaining X-ray diffraction quality crystals is highly unpredictable (see previous enablement rejection with regard to the unpredictability associated with making X-ray diffraction quality crystals), the scope of crystals as explained above for each claim is not commensurate with the disclosure provided in the instant application which is limited to 4 X-ray diffraction quality crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. In addition, as explained in the previous enablement rejection, the general knowledge in the art teaches that an amino acid sequence cannot be theoretically translated into a biologically relevant 3-D structure. Also, the Case 4 of the Trilateral Project WM4, is not analogous to the fact

patterns of this instant application with regard to the protein structure of LXR β *Ligand Binding Domain, having any unit cell dimensions and any bond angles* (emphasis added). Even assuming *arguendo* that the crystal of claim 1 (a) meets the criteria as set forth in Case 4 of the Trilateral Project WM4 with regard to the LXR β LBD which *consists of the recited amino acids*, there is no limitations on unit cell dimensions of the crystal of Claim 1 (a), which clearly fails to meet the criteria as set forth in the Case 4 of the Trilateral Project WM4.

Regarding claims 8-10, contrary to Applicants' allegation, the LXR β *ligand binding domain has any amino acid residues of LXR β that are capable of binding a ligand* (see above 112 2nd paragraph rejection for the claim interpretation). As such, claims 8-10 fail to meet the criteria as set forth in the Case 4 of the Trilateral Project WM4 especially with regard to the specific structure of the LXR β *ligand binding domain which undefined* (emphasis added).

For these reasons, it would require undue experimentation for one of skill in the art make and use the scope of crystals as claimed because one would have to painstakingly determine which of the genera of crystals as described above represent the biologically relevant 3-D structures so that structural studies can be performed in order to determine "compounds which are likely to bind to the receptor based on their three dimensional shape in particular the ligand binding domain of the LXR beta" (see page 4 of the specification for the intended use of the claimed invention). It is noted by the Examiner that the specification only describes 4 X-ray diffraction quality crystals (2 crystals with space group P2₁2₁2₁, 1 crystal with space group P6₁22, and 1 crystal with

space group $P2_12_12$ having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claim Rejections - 35 U.S.C. § 102

The previous rejection of Claims 1, 3, 11, 12, 29-32, 35, 43 and 45 under 35 U.S.C. § 102(e) as anticipated by Bledsoe et al. (US Patent Application No. 10/418,007, (effective filing date 04/26/2002)) is withdrawn because the crystal of a ligand binding domain of human LXR beta consisting of contiguous amino acid residues 214-462, bound to N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide, belonging to space group $P2_12_12$ taught by Bledsoe et al. is different from Applicants' crystal of the ligand binding domain of human LXR beta consisting of 220-461 or 213-461 of SEQ ID NO: 1.

Conclusion

Claims 3-7, 31, 32, 35 and 42 are objected to, and Claims 1, 2, 8-12, 29, 30, 40, 41 and 43-45 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

This office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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